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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/234,208	01/20/1999	JONI KRISTIN DOHERTY	49321-1	6406

22504 7590 07/26/2006

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EXAMINER	
UNGAR, SUSAN NMN	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 07/26/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/234,208	DOHERTY ET AL.	
	Examiner	Art Unit	
	Susan Ungar	1642	

– The MAILING DATE of this communication appears on the cover sheet with the correspondence address –

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *03 May 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-3,8-10,18-20 and 27-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-3, 8-10, 18-20, 27-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1)☐ Notice of References Cited (PTO-892)

2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3)☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 9/24/05, 5/3/06

4)☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

5)☐ Notice of Informal Patent Application (PTO-152)

6)☐ Other: _____.

1. The Amendment filed May 3, 2006 in response to the Office Action of November 3, 2005 is acknowledged and has been entered. Previously pending claims 18 and 20 have been amended. Claims 1-3, 8-10, 18-20, 27-30 are currently being examined.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. The following rejections are being maintained:

Claim Rejections - 35 USC 112

4. Claims 1-3, 8-9, 18-20, 29-30 remain rejected under 35 USC 112, first paragraph for the reasons previously set forth in the paper mailed November 3, 2005, Section 6, pages 3-7.

Applicant argues that general techniques for isolating, expressing and testing polypeptides comprising all or part of the sequence of p68HER-2 are provided in the specification and known to the skilled artisan and therefore, it would not be undue experimentation to make and use the claimed subject matter. The argument has been considered but has not been found persuasive because, as previously set forth, in order to meet the enablement requirement of 35 USC 112, first paragraph, the specification must teach how to make the claimed invention and that, in particular, the court found in (*Rochester v. Searle*, 358 F.3d 916, Fed Cir., 2004) that screening assays, instantly suggested by Applicant, are not sufficient to enable an invention because they are merely a wish or plan for obtaining the claimed chemical invention.

Applicant argues that the claims are within the scope of what is taught in the specification, that is a genus of polypeptides of p68HER-2 that includes the particular claimed polypeptides. The argument has been considered but has not

been found persuasive because the specification does not enable the scope of the claimed invention for the reasons of record. In particular, as previously set forth, the specification as originally filed does not provide information drawn to the amino acids critical for binding to HER-2, does not provide information drawn to the effects of the undefined and unlimited amino acids which "comprise" the claimed species on the binding to HER-2, does not provide information drawn to the folding of the broadly claimed peptides.

Applicant argues that the level of skill is recognized to be high. The argument has been considered but has not been found persuasive because despite the level of skill in the HER-2 arts, given the lack of guidance in the specification as originally filed, the scope of the claims is not enabled.

Applicant argues that a broad body of knowledge was available and known about HER-2 at the time the invention was made wherein truncated variants of HER-2 were known and analyzed for function wherein a variety of published protocols for the identification, production and/or analysis of truncated receptor tyrosine kinase products were known in the art. The argument has been considered but has not been found persuasive because, as set forth previously and above, in order to meet the enablement requirement of 35 USC 112, first paragraph, the specification must teach how to make the claimed invention and that, in particular, the court found in (*Rochester v. Searle*, 358 F.3d 916, Fed Cir., 2004) that screening assays, instantly suggested by Applicant, are not sufficient to enable an invention because they are merely a wish or plan for obtaining the claimed chemical invention.

Applicant argues that the teachings of the specification and working examples enable the claimed invention. In particular, the specification teaches the

detailed structural and functional characterization of a naturally occurring inhibitor of HER-2, p68Her-2 and that the binding affinity of p68HER-2 resides in the novel proline rich ECDIIIa domain. The argument has been considered but has not been found persuasive since the claims are not drawn to the novel peptide with high affinity binding, but rather are drawn to a polypeptide comprising 59/69 to 79 contiguous residues of SEQ ID NO:1 and for the reasons of record, the effect of alterations on the affinity of binding of the polypeptide cannot be predicted, in particular because the specification teaches that "It was discovered that the 79 amino acid polypeptide [SEQ ID NO. 1] exhibited surprising high affinity binding properties to the ECD of HER-2. Moreover, the site of such binding is different and unaffected by the site of binding of a marketed humanized monoclonal antibody (HERCEPTIN.RTM.). Therefore, the high binding affinity enables the 79 amino acid polypeptide to function as a targeting molecule to tumor cells expressing HER-2."

Applicant reiterates the teachings of the Working Examples 1, 4, 5, 9, 10 wherein the specification provides characterization, cloning, purification and function of the 79 amino acid fragment that has been demonstrated to have "exhibited surprising high affinity binding properties to the ECD of HER-2". Given the surprising high affinity binding properties of the 79 amino acid fragment, the broadly claimed invention is not enabled.

Applicant argues that given the teaching in the art together with the teaching in the specification, it is not unpredictable that p68HER2 fragments can be generated and tested for their ability to bind and those that bind identified. The argument has been considered but has not been found persuasive because the claimed invention is not limited to fragments of p68HER2 and thus applicant is

arguing limitations not recited in the claims as currently constituted. Further, as set forth previously and above, in order to meet the enablement requirement of 35 USC 112, first paragraph, the specification must teach how to make the claimed invention and that, in particular, the court found in (*Rochester v. Searle*, 358 F.3d 916, Fed Cir., 2004) that screening assays, instantly suggested by Applicant, are not sufficient to enable an invention because they are merely a wish or plan for obtaining the claimed chemical invention.

Applicant argues that the claims are drawn to polypeptides of SEQ ID NO:1 or SEQ ID NO:2 or fragments thereof that bind to p185Her-2 with a binding affinity of $10^8 M^{-1}$ and that this functional limitation naturally excludes polypeptides that would not bind to p185HER-2 because they no longer contain the binding site and/or the polypeptides are folded in such a way as to 'mask' the binding site. Further, given that the specification teaches the entire sequence of the polypeptides and demonstrates assays, it is within the skill of the art to systematically remove residues and test for activity.

The argument has been considered but has not been found persuasive because although the claims exclude polypeptides that would not bind to p185HER-2 at the claimed binding affinity, for the reasons of record, drawn specifically to the teachings of Bowie et al, Rudikoff et al, Burgess et al, the specification does not teach how to make the claimed invention. Further, as set forth previously and above, in order to meet the enablement requirement of 35 USC 112, first paragraph, the specification must teach how to make the claimed invention and that, in particular, the court found in (*Rochester v. Searle*, 358 F.3d 916, Fed Cir., 2004) that screening/testing assays, instantly suggested by

Applicant, are not sufficient to enable an invention because they are merely a wish or plan for obtaining the claimed chemical invention.

Applicant argues that given that the specification teaches that a polypeptide comprising SEQ ID NO:1, that is the his-tagged ECDIIIa peptide, functions as claimed, it is not unpredictable that other polypeptide fragments also bind p185HER-2 and again urges that polypeptides produced can be tested. The argument has been considered but has not been found persuasive because Applicant is arguing limitations not recited in the claims as currently constituted and because although other fragments might bind to p185HER-2, the claims are not simply drawn to binding to p185HER-2$_{ex}$, but rather are drawn to binding to p185HER-2, with an affinity constant of $10^8 M^{-1}$ and for the reasons of record, the effects of truncations, additions on the binding of the fragment to p185HER-2 cannot be predicted. Further, as set forth previously and above, in order to meet the enablement requirement of 35 USC 112, first paragraph, the specification must teach how to make the claimed invention and that, in particular, the court found in (*Rochester v. Searle*, 358 F.3d 916, Fed Cir., 2004) that screening/testing assays, instantly suggested by Applicant, are not sufficient to enable an invention because they are merely a wish or plan for obtaining the claimed chemical invention.

Applicant argues that the (1) claims refer to contiguous residues, (2) the specification teaches that p68HER-2 and the ECDIIIa subregion thereof both bind with very high affinity to HER-2. Significantly, the fact that high affinity binding is retained by the 79 amino acids of ECDIIIa would not suggest to one skilled in the art that the entire 79 amino acids are essential for high affinity binding, but rather only that the minimal region sufficient for binding is contained therein, (3) Applicant's teach a region and further teach how to rapidly identify operative

embodiments and the functional binding limitation serves to ensure that the scope of the claimed subject matter is commensurate with the teachings of the specification.

The argument has been considered but has not been found persuasive because (1')(2') for the reasons set forth previously and above, the specification does not teach how to make the claimed invention, (2') the specification does not teach that both p68HER-2 and the ECDIIIa subregion bind with very high affinity to HER-2. Although the specification teaches that p68HER-2 specifically binds to HER-2, it teaches that "the unique ECDIIIa peptide binds with high affinity" (p. 8), (3') for the reasons set forth previously and above, the specification does not teach the residues critical to invention and therefore does not teach how to make the claimed invention.

Applicant argues that several of Applicant's copending applications disclose specific active polymorphic variants of Herstatin that correspond to non-conservative amino acid substitutions and that 6 of these non-conservative variable positions occur within the first 21 amino acids, confirming the reasonable basis for claiming regions of at least 50 contiguous amino acids. The argument has been considered but has not been found persuasive because Examiner is unable to evaluate the information given that Applicant does not point to the copending applications or page and line numbers within those applications where this information may be found.

Applicant reiterates arguments drawn to the his-tagged ECDIIIa fusion protein. The argument has been considered above and not found persuasive for the reasons set forth above.

The arguments have been considered but have not been found persuasive and the rejection is maintained.

Applicant further argues that the instant rejection is not a new ground of rejection, but is actually an almost identical rejection as set forth in the Office Action dated August 1, 2001 which was obviated by the response and amendments filed 20 February 2002 as indicated by the withdrawal of the rejection in the office action dated May22, 2002 and that the present rejection is inconsistent with the previous prosecution. The argument has been considered but has not been found persuasive because the rejection is not in fact "almost identical" because the rejection is not drawn to "non-contiguous" amino acids, but rather is drawn to the unpredictability of the protein chemistry, lack of teaching of the critical amino acid residues, lack of teaching on effects of conformation. Further, it is noted that Applicant overcame the rejections drawn to claims 8 and claims dependent upon claim 8 by amending the claims to include new matter, that is the limitation drawn to an affinity constant of $10^8 M^{-1}$ for polypeptides comprising SEQ ID NO:2 and polypeptides comprising 80-419 contiguous amino acids of SEQ ID NO:2. The new matter issue will be dealt with below.

Applicant reiterates arguments that production of polypeptides that bind to the ECD of p185Her-2 is predictable. The argument was considered previously and for the reasons set forth above, was not found persuasive.

Applicant argues that the fact pattern of Rochester v. Searle is misplaced because it addresses the written description and not enablement, which is distinct from the written description requirement and further that the fact pattern pertinent to the findings in *Rochester v. Searle* are distinct from the fact pattern of the instant application. In particular, the claims at issue in *Rochester v. Searle* are drawn to

screening assays to determine whether a particular drug selectively inhibited the activity of COX-2 without inhibiting COX-1 wherein the patent did not disclose any compound that would function as claimed, nor provided any suggestion as to how such a compound would be made. The instant claims are not directed to screening assays, but are directed to polypeptides wherein the application provides polypeptides, their sequence and methods for testing their binding, Thus, the findings in *Rochester v. Searle* do not lead to a lack of enablement.

The argument has been considered but has not been found persuasive because, although the claims are drawn to polypeptides and the specification teaches methods of screening, those methods of screening are drawn to screening for polypeptides that bind to HER2-neu and not to screening for the subsequence of p68HER-2 that is critical to the claimed binding affinity constant of $10^8 M^{-1}$. Further, although the instant specification teaches a single example of a polypeptide with the claimed binding affinity constant, given that the critical residues are not taught, the only recourse that the practitioner is left with in order to determine those critical residues is by the use of screening assays as suggested by Applicant and thus the teachings of the court in *Rochester v. Searle* is relevant to the instant rejection and although the fact patterns are different, the issues are the same. In particular, even if screening assays drawn to the claimed binding affinity constant of $10^8 M^{-1}$ were taught in the specification, those screening assays would merely be a wish or plan for obtaining the claimed chemical invention.

Applicant's statement on public policy considerations is noted.

The arguments have been considered but have not been found persuasive and the rejection is maintained.

5. Claims 18-20, 29-30 remain rejected under 35 USC 112, first paragraph for the reasons previously set forth in the paper mailed November 3, 2005, Section 7, pages 7-10.

Applicant argues that for the reasons set forth above, it would not require undue experimentation for a person of skill in the art to make and use the claimed pharmaceutical compositions. Applicant points specifically to anti-tumor cell activity by p68HER-2 in an assay of assessing anchorage independent growth of cells in soft agar on p. 13, lines 5-23 and that given the high degree of knowledge that was available at the time of the filing of the instant application in combination with the teachings of the specification, the broadly claimed invention is enabled. The argument has been considered but has not been found persuasive because the issue raised is not drawn to SEQ ID NO:2/p68HER-2 which was used in the assay disclosed on p. 13, lines 5-23, but rather is drawn to the claims that include fragments of SEQ ID NO:2, SEQ ID NO:1 and fragments of SEQ ID NO:1. For the reasons previously set forth the specification as originally filed is not enabling for a pharmaceutical composition comprising species other than p68HER-2/SEQ ID NO:2.

Applicant argues that the Examiner has provided no evidence that the polypeptides cannot be formulated as a pharmaceutical composition and so used and the claims recite that the polypeptides have a recited binding affinity which the exemplified polypeptides possess. The argument has been considered but has not been found persuasive because although it is clear that the polypeptides can be formulated as pharmaceutical compositions, the art recognizes the unpredictability of the cancer treatment arts and in the absence of objective evidence, for the

reasons previously set forth, no one of ordinary skill in the art would believe it more likely than not that the broadly claimed invention would function as claimed.

The arguments have been considered but have not been found persuasive and the rejection is maintained.

New Grounds of Rejection

Claim Rejections - 35 USC 112

6. Claims 8-10, 18, 29, 30 are rejected under 35 USC 112, first paragraph as the specification does not contain a written description of the claimed invention. The limitation of an isolated polypeptide comprising the amino acid sequence of SEQ ID NO:2 or a fragment thereof wherein the polypeptide binds to the extracellular domain of HER-2 with a binding affinity constant of 10^8M^{-1} has no clear support in the specification and the claims as originally filed. Applicant cited support for the instantly claimed limitation in the paper submitted February 20, 2002. In particular, the paper submitted discloses that Applicant amends the claims to overcome a written description rejection and states specifically states that the claims "have been amended to recite limiting functional language that the encoded polypeptide binds to the extracellular domain (ECD) of HER-2 with an affinity binding constant of 10^8M^{-1} and points to support for the newly added claim limitation at page 22, example 9 and figure 5. However, a review of the specification cited support does not reveal any statement drawn to a binding affinity constant of 10^8M^{-1} for an isolated polypeptide comprising the amino acid sequence of SEQ ID NO:2 or a fragment thereof. The subject matter claimed in claims 8-10, 18, 29, 30 broadens the scope of the invention as originally disclosed in the specification.

7. Claims 8-10, 18 are rejected under 35 USC 112, first paragraph as the specification does not contain a written description of the claimed invention. The limitation of "at least one N-linked glycosylation site is present" has no clear support in the specification and the claims as originally filed. Although Applicant added the limitation in the paper submitted February 20, 2002, a review of that paper did not reveal support for the newly claimed limitation. A review of the specification revealed that there is no recitation in the specification as originally filed of the phrase "at least one". The subject matter claimed in claims 8-10, 18, broadens the scope of the invention as originally disclosed in the specification.

8. Claims 18 and 30 are rejected under 35 USC 112, first paragraph as the specification does not contain a written description of the claimed invention. The limitation of "combination thereof with the provision that where the composition comprises the monoclonal antibody it also comprises at least one of the agents of (a) and (b) no clear support in the specification and the claims as originally filed. Applicant cited support for the instantly claimed limitation in the paper submitted December 29, 2003. In particular, the paper submitted discloses that Applicant amends the claims to overcome the rejections of record and points to support for the newly added claim limitation at page pages 9-10 drawn to pharmaceutical compositions. A review of pages 9-10 reveals that the specification teaches that "The present invention further provides a pharmaceutical composition for treating solid tumors that overexpress HER-2, comprising an agent selected from the group consisting of (a) an isolated polypeptide having from about 50 to 79 amino acids taken from the sequence of SEQ ID NO:1, wherein the polypeptide binds to the extracellular domain ECD of HER-2 at an affinity of at least 10^8, (b) an isolated and glycosylated polypeptide having from about 300 to 419 amino acids taken from the sequence of SEQ ID NO:2, wherein the C terminal 79 amino acids are present, and wherein at least three N-linked glycosylation sites are present, (c) a

monoclonal antibody that binds to the ECD of HER-2, and (d) combinations thereof, with the proviso that the agent cannot be the monoclonal antibody alone"

However, the teaching is not drawn to an agent comprising either SEQ ID NO:1 or SEQ ID NO:2 in combination with the monoclonal antibody. The subject matter claimed in claims 18 and 30 broadens the scope of the invention as originally disclosed in the specification.

9. Claims 9 is rejected under 35 USC 112, first paragraph as the specification does not contain a written description of the claimed invention. The limitation of an isolated polypeptide, wherein the isolated polypeptide is from about 350 to 419 contiguous residues in length and three N-linked glycosylation sites are present has no clear support in the specification and the claims as originally filed. Although Applicant added the limitation in the paper submitted February 20, 2002, a review of that paper did not reveal support for the newly claimed limitation. A review of the specification revealed support for 'the isolated polypeptide is from about 350 to 419 amino acids in length and four N-linked glycosylation sites are present, as well as support for "an isolated and glycosylated polypeptides having from about 80 to 419 amino acids.....wherein at least three N-linked glycosylation sites are present, but no support for the instantly claimed limitation. The subject matter claimed in claims 9 broadens the scope of the invention as originally disclosed in the specification.

10. Claims 27 and 28 are free of the art and allowable.

11. All other objections and rejections set forth in the previous office action are hereby withdrawn.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is

(571) 272-0837. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at 571-272-0787. The fax phone number for this Art Unit is (571) 273-8300.

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1642.

Susan Ungar
Primary Patent Examiner
July 10, 2006